

(c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the library of ligands identified in (a) with the linker or mixture of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands; and

(d) assaying the multimeric ligand compounds produced in the library prepared in (c) above to identify multimeric ligand compounds possessing multibinding properties.

5 3. The method according to Claim 1 or 2 wherein the preparation of the multimeric ligand compound library is achieved by either the sequential or concurrent combination of the two or more stoichiometric equivalents of the ligands identified in (a) with the linkers identified in (b).

10 4. The method according to Claim 3 wherein the multimeric ligand compounds comprising the multimeric ligand compound library are dimeric.

 5. The method according to Claim 4 wherein the dimeric ligand compounds comprising the dimeric ligand compound library are heterodimeric.

15 6. The method according to Claim 5 wherein the heterodimeric ligand compound library is prepared by sequential addition of a first and second ligand.

20 7. The method according to Claim 1 or 2 wherein, prior to procedure (d), each member of the multimeric ligand compound library is isolated from the library.

25 8. The method according to Claim 7 wherein each member of the library is isolated by preparative liquid chromatography mass spectrometry (LCMS).

 9. The method according to Claim 1 or Claim 2 wherein the linker or linkers employed are selected from the group comprising flexible linkers, rigid linkers, hydrophobic linkers, hydrophilic linkers, linkers of different geometry,

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acidic linkers, basic linkers, linkers of different polarization and/or polarizability and amphiphilic linkers.

10. The method according to Claim 9 wherein the linkers comprise
5 linkers of different chain length and/or having different complementary reactive groups.

11. The method according to Claim 10 wherein the linkers are selected
10 to have different linker lengths ranging from about 2 to 100Å.

12. The method according to Claim 1 or 2 wherein the ligand or
mixture of ligands is selected to have reactive functionality at different sites on
said ligands.

13. The method according to Claim 12 wherein said reactive
15 functionality is selected from the group consisting of carboxylic acids, carboxylic acid halides, carboxyl esters, amines, halides, pseudohalides, isocyanates, vinyl unsaturation, ketones, aldehydes, thiols, alcohols, anhydrides, boronates, and precursors thereof wherein the reactive functionality on the ligand is selected to be
20 complementary to at least one of the reactive groups on the linker so that a covalent linkage can be formed between the linker and the ligand.

14. The method according to Claim 1 or Claim 2 wherein the
multimeric ligand compound library comprises homomeric ligand compounds.

15. The method according to Claim 1 or Claim 2 wherein the
multimeric ligand compound library comprises heteromeric ligand compounds.

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16. A library of multimeric ligand compounds which may bind a cellular receptor and may possess multivalent properties which library is prepared by the method comprising:

- (a) identifying a ligand or a mixture of ligands which bind a cellular receptor wherein each ligand contains at least one reactive functionality;
- (b) identifying a library of linkers wherein each linker in said library comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand; and
- (c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the ligand or mixture of ligands identified in (a) with the library of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands.

17. A library of multimeric ligand compounds which may bind a cellular receptor and may possess multivalent properties which library is prepared by the method comprising:

- (a) identifying a library of ligands wherein each ligand binds a cellular receptor and contains at least one reactive functionality;
- (b) identifying a linker or mixture of linkers wherein each linker comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand; and
- (c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the library of ligands identified in (a) with the linker or mixture of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands.

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18. The library according to Claim 16 or Claim 17 wherein the linker or linkers employed are selected from the group comprising flexible linkers, rigid linkers, hydrophobic linkers, hydrophilic linkers, linkers of different geometry, acidic linkers, basic linkers, linkers of different polarization and/or polarizability and amphiphilic linkers.

19. The library according to Claim 18 wherein the linkers comprise linkers of different chain length and/or having different complementary reactive groups.

20. The library according to Claim 19 wherein the linkers are selected to have different linker lengths ranging from about 2 to 100Å.

21. The library according to Claim 16 or 17 wherein the ligand or mixture of ligands is selected to have reactive functionality at different sites on said ligands.

22. The library according to Claim 21 wherein said reactive functionality is selected from the group consisting of carboxylic acids, carboxylic acid halides, carboxyl esters, amines, halides, pseudohalides, isocyanates, vinyl unsaturation, ketones, aldehydes, thiols, alcohols, anhydrides, boronates, and precursors thereof wherein the reactive functionality on the ligand is selected to be complementary to at least one of the reactive groups on the linker so that a covalent linkage can be formed between the linker and the ligand.

23. The library according to Claim 16 or Claim 17 wherein the multimeric ligand compound library comprises homomeric ligand compounds.

(f) evaluating what molecular constraints imparted or are consistent with imparting enhanced multibinding properties to the multimeric compound or compounds found in the second collection or iteration recited in (e) above;

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(g) optionally repeating steps (e) and (f) to further elaborate upon said molecular constraints.

26. The method according to Claim 25 wherein steps (e) and (f) are repeated from 2-50 times.

27. The method according to Claim 26 wherein steps (e) and (f) are repeated from 5-50 times.

28. A multi-binding compound comprising 2 to 10 ligands which may be the same or different and which are covalently attached to a linker or linkers which may be the same or different, each of said ligands comprising a ligand domain capable of binding to a cellular receptor, with the following provisos:

(a) the ligand does not bind to a 5-HT1b receptor, a 5-HT1d receptor, a 5-HT1f receptor, a β 2-adrenergic receptor, a M2 muscarinic receptor, a M3 muscarinic receptor or an opioid receptor ;

(b) when a first ligand is a peptide, then additional ligands do not bind to neurokinin 2 receptor or are not peptides;

(c) when the multibinding compound comprises two ligands having a tetraazacrown capable of binding to a CCR5 or CXCR4 receptor, then the linker is not a polymethylene group;

(d) when the multibinding compound comprises two ligands having a hexestrol moiety capable of binding to an estrogen receptor, then the linker is not a polymethylene group;

(e) when the multibinding compound is capable of binding to an α -adrenergic receptor, then a ligand is not N,N'-(bis-(5-aminopentyl)cystamine (APC) or an analog thereof;

(g) when a first ligand is 2-allylphenyl, 4-(2-methoxyethyl)phenyl, 1-naphthyl, or 4-methoxyphenyl moiety and is capable of binding to the β 1-adrenergic receptor, then the linker is not a Jeffamine;

(i) when a first ligand is a mannose moiety and is capable of binding to a selectin, then the linker is not a poly(arylene) group;

(j) when a first ligand is a 2-(3, 4-dihydroxybenzyl pyrrolidine) moiety and is capable of binding to a dopamine receptor and a linker is an alkylene group, then the second ligand is not a 2-(3, 4-dihydroxybenzyl pyrrolidine) or an N-ethyl (3, 4-dihydroxyphenethyl amine) moiety; and

(k) when a first ligand is a 2-phenylbenzimidazole moiety and is capable of binding a dopamine receptor and a linker is an alkylene, alkenylene or arylalkylene group then a second ligand is not a 2-phenylbenzimidazole or a benzimidazole moiety.

29. A multi-binding compound represented by formula I:



wherein each L is independently selected from ligands comprising a ligand domain capable of binding to a receptor; X is a linker; p is an integer of from 2 to 10; q is an integer of from 1 to 20 and salts thereof;

with the following provisos:

(a) the ligand is not capable of binding to a 5-HT1b receptor, a 5-HT1d receptor, a 5-HT1f receptor, a beta-2-adrenergic receptor, a M2 muscarinic receptor, M3 muscarinic receptor or an opioid receptor;

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(b) when, in formula I, p is 2, q is 1 and the first L is a peptide, then the second L does not bind to neurokinin 2 receptor or is not a peptide;

(c) when in formula I, X is a polymethylene group, p is 2 and q is 1, then L is not a tetraazacrown moiety capable of binding to a CCR5 or CXCR4 receptor;

(d) when in formula I, X is a polymethylene group, p is 2 and q is 1, then L is not hexestrol moiety capable of binding to an estrogen receptor;

(e) when in formula I, p is 2 and q is 1, then L is not an analog of N,N'-(bis-(5-aminopentyl)cystamine (APC) capable of binding to an α -adrenergic receptor;

(f) when in formula I, X is a polymethylene or poly(ethyleneoxide) group, p is 2 and q is 1, then L is not a 1-(aryloxy)-2-hydroxypropanolamine moiety capable of binding to an β 1-adrenergic receptor;

(g) when in formula I, X is a Jeffamine, p is 2 and q is 1, then L is not a 2-allylphenyl, 4-(2-methoxyethyl)phenyl, 1-naphthyl, or 4-methoxyphenyl moiety capable of binding to an β 1-adrenergic receptor;

(h) when in formula I, X is a polymethylene or poly(ethyleneoxide) group, p is 2 and q is 1, then L is not a sLeX moiety capable of binding to a selectin;

(i) when in formula I, X is a poly(arylene) group, p is 2 or 3 and q is 1, then L is not a mannose moiety capable of binding to a selectin;

(j) when in formula I, X is an alkylene group, p is 2, q is 1 and the first L is a 2-(3, 4-dihydroxybenzyl pyrrolidine) moiety capable of binding to a dopamine receptor, then the second L is not a 2-(3, 4-dihydroxybenzyl pyrrolidine) or an N-ethyl (3, 4-dihydroxyphenethyl amine) moiety capable of binding to a dopamine receptor; and

(k) when in formula I, X is an alkylene, alkenylene or arylalkylene group, p is 2, q is 1 and the first L is a 2-phenylbenzimidazole moiety capable of

30. The multibinding compound of Claim 2 wherein q is less than p .

(a) the ligand does not bind to a 5-HT1b receptor, a 5-HT1d receptor, a 5-HT1f receptor, a β 2-adrenergic receptor, a M2 muscarinic receptor, a M3 muscarinic receptor or an opioid receptor ;

(b) when a first ligand is a peptide, then additional ligands do not bind to neurokinin 2 receptor or are not peptides;

(c) when the multibinding compound comprises two ligands having a tetraazacrown capable of binding to a CCR5 or CXCR4 receptor, then the linker is not a polymethylene group;

(d) when the multibinding compound comprises two ligands having a hexestrol moiety capable of binding to an estrogen receptor, then the linker is not a polymethylene group;

(e) when the multibinding compound is capable of binding to an α -adrenergic receptor, then a ligand is not N,N'-(bis-(5-aminopentyl)cystamine (APC) or an analog thereof;

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(f) when a first ligand is 1-(aryloxy)-2-hydroxypropanolamine moiety and is capable of binding to an β -adrenergic receptor, then a linker is not a polymethylene or poly(ethyleneoxide) group;

(g) when a first ligand is 2-allylphenyl, 4-(2-methoxyethyl)phenyl, 1-naphthyl, or 4-methoxyphenyl moiety and is capable of binding to the β 1-adrenergic receptor, then the linker is not a Jeffamine;

(h) when a first ligand is a sLeX moiety and is capable of binding to a selectin, then the linker is not a polymethylene or poly(ethyleneoxide) group;

(i) when a first ligand is a mannose moiety and is capable of binding to a selectin, then the linker is not a poly(arylene) group;

(j) when a first ligand is a 2-(3, 4-dihydroxybenzyl pyrrolidine) moiety and is capable of binding to a dopamine receptor and a linker is an alkylene group, then the second ligand is not a 2-(3, 4-dihydroxybenzyl pyrrolidine) or an N-ethyl (3, 4-dihydroxyphenethyl amine) moiety; and

(k) when a first ligand is a 2-phenylbenzimidazole moiety and is capable of binding a dopamine receptor and a linker is an alkylene, alkenylene or arylalkylene group then a second ligand is not a 2-phenylbenzimidazole or a benzimidazole moiety.

32 A pharmaceutical composition comprising a pharmaceutically acceptable excipient and an effective amount of a multi-binding compound represented by formula I:



wherein each L is independently selected from ligands comprising a ligand domain capable of binding to a cellular receptor mediating mammalian or avian pathologic conditions; X is a linker; p is an integer of from 2 to 10; q is an integer of from 1 to 20;

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with the following provisos:

(a) the ligand is not capable of binding to a 5-HT1b receptor, a 5-HT1d receptor, a 5-HT1f receptor, a beta-2-adrenergic receptor, a M2 muscarinic receptor, M3 muscarinic receptor or an opioid receptor;

(b) when, in formula I, p is 2, q is 1 and the first L is a peptide, then the second L does not bind to neurokinin 2 receptor or is not a peptide;

(c) when in formula I, X is a polymethylene group, p is 2 and q is 1, then L is not a tetraazacrown moiety capable of binding to a CCR5 or CXCR4 receptor;

(d) when in formula I, X is a polymethylene group, p is 2 and q is 1, then L is not hexestrol moiety capable of binding to an estrogen receptor;

(e) when in formula I, p is 2 and q is 1, then L is not an analog of N,N'-(bis-(5-aminopentyl)cystamine (APC) capable of binding to an α -adrenergic receptor;

(f) when in formula I, X is a polymethylene or poly(ethyleneoxide) group, p is 2 and q is 1, then L is not a 1-(aryloxy)-2-hydroxypropanolamine moiety capable of binding to an β 1-adrenergic receptor;

(g) when in formula I, X is a Jeffamine, p is 2 and q is 1, then L is not a 2-allylphenyl, 4-(2-methoxyethyl)phenyl, 1-naphthyl, or 4-methoxyphenyl moiety capable of binding to an β 1-adrenergic receptor;

(h) when in formula I, X is a polymethylene or poly(ethyleneoxide) group, p is 2 and q is 1, then L is not a sLeX moiety capable of binding to a selectin;

(i) when in formula I, X is a poly(arylene) group, p is 2 or 3 and q is 1, then L is not a mannose moiety capable of binding to a selectin;

(j) when in formula I, X is an alkylene group, p is 2, q is 1 and the first L is a 2-(3, 4-dihydroxybenzyl pyrrolidine) moiety capable of binding to a dopamine receptor, then the second L is not a 2-(3, 4-dihydroxybenzyl pyrrolidine)

or an N-ethyl (3, 4-dihydroxyphenethyl amine) moiety capable of binding to a dopamine receptor; and

(k) when in formula I, X is an alkylene, alkenylene or arylalkylene group, p is 2, q is 1 and the first L is a 2-phenylbenzimidazole moiety capable of binding to a dopamine receptor, then the second L is not a 2-phenylbenzimidazole or a benzimidazole moiety capable of binding to a dopamine receptor, and pharmaceutically acceptable salts thereof.

33. A method for treating a mammalian or avian pathologic condition mediated by cellular receptors which method comprises administering to said mammal or bird an effective amount of a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a multi-binding compound or a pharmaceutically acceptable salt thereof comprising 2 to 10 ligands which may be the same or different and which are covalently attached to a linker or linkers which may be the same or different, each of said ligands comprising a ligand domain capable of binding to a cellular receptor mediating mammalian or avian pathologic conditions;

with the following provisos:

(a) the ligand does not bind to a 5-HT1b receptor, a 5-HT1d receptor, a 5-HT1f receptor, a β 2-adrenergic receptor, a M2 muscarinic receptor, a M3 muscarinic receptor or an opioid receptor ;

(b) when a first ligand is a peptide, then additional ligands do not bind to neurokinin 2 receptor or are not peptides;

(c) when the multibinding compound comprises two ligands having a tetraazacrown capable of binding to a CCR5 or CXCR4 receptor, then the linker is not a polymethylene group;

(d) when the multibinding compound comprises two ligands having a hexestrol moiety capable of binding to an estrogen receptor, then the linker is not a polymethylene group;

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(e) when the multibinding compound is capable of binding to an α -adrenergic receptor, then a ligand is not N,N'-(bis-(5-aminopentyl)cystamine (APC) or an analog thereof;

(f) when a first ligand is 1-(aryloxy)-2-hydroxypropanolamine moiety and is capable of binding to an β -adrenergic receptor, then a linker is not a polymethylene or poly(ethyleneoxide) group;

(g) when a first ligand is 2-allylphenyl, 4-(2-methoxyethyl)phenyl, 1-naphthyl, or 4-methoxyphenyl moiety and is capable of binding to the β 1-adrenergic receptor, then the linker is not a Jeffamine;

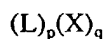
(h) when a first ligand is a sLeX moiety and is capable of binding to a selectin, then the linker is not a polymethylene or poly(ethyleneoxide) group;

(i) when a first ligand is a mannose moiety and is capable of binding to a selectin, then the linker is not a poly(arylene) group;

(j) when a first ligand is a 2-(3, 4-dihydroxybenzyl pyrrolidine) moiety and is capable of binding to a dopamine receptor and a linker is an alkylene group, then the second ligand is not a 2-(3, 4-dihydroxybenzyl pyrrolidine) or an N-ethyl (3, 4-dihydroxyphenethyl amine) moiety; and

(k) when a first ligand is a 2-phenylbenzimidazole moiety and is capable of binding a dopamine receptor and a linker is an alkylene, alkenylene or arylalkylene group then a second ligand is not a 2-phenylbenzimidazole or a benzimidazole moiety.

34. A method for treating a mammalian or avian pathologic condition mediated by cellular receptors which method comprises administering to said mammal or bird an effective amount of a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a multi-binding compound represented by formula I:



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wherein each L is independently selected from ligands comprising a ligand domain capable of binding to one or more cellular receptors mediating mammalian pathologic conditions; X is a linker; p is an integer of from 2 to 10; q is an integer of from 1 to 20;

with the following provisos:

(a) the ligand is not capable of binding to a 5-HT1b receptor, a 5-HT1d receptor, a 5-HT1f receptor, a beta-2-adrenergic receptor, a M2 muscarinic receptor, M3 muscarinic receptor or an opioid receptor;

(b) when, in formula I, p is 2, q is 1 and the first L is a peptide, then the second L does not bind to neurokinin 2 receptor or is not a peptide;

(c) when in formula I, X is a polymethylene group, p is 2 and q is 1, then L is not a tetraazacrown moiety capable of binding to a CCR5 or CXCR4 receptor;

(d) when in formula I, X is a polymethylene group, p is 2 and q is 1, then L is not hexestrol moiety capable of binding to an estrogen receptor;

(e) when in formula I, p is 2 and q is 1, then L is not an analog of N,N'-(bis-(5-aminopentyl)cystamine (APC) capable of binding to an α -adrenergic receptor;

(f) when in formula I, X is a polymethylene or poly(ethyleneoxide) group, p is 2 and q is 1, then L is not a 1-(aryloxy)-2-hydroxypropanolamine moiety capable of binding to an β 1-adrenergic receptor;

(g) when in formula I, X is a Jeffamine, p is 2 and q is 1, then L is not a 2-allylphenyl, 4-(2-methoxyethyl)phenyl, 1-naphthyl, or 4-methoxyphenyl moiety capable of binding to an β 1-adrenergic receptor;

(h) when in formula I, X is a polymethylene or poly(ethyleneoxide) group, p is 2 and q is 1, then L is not a sLeX moiety capable of binding to a selectin;

(i) when in formula I, X is a poly(arylene) group, p is 2 or 3 and q is 1, then L is not a mannose moiety capable of binding to a selectin;

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(c) when the multibinding compound comprises two ligands having a tetraazacrown capable of binding to a CCR5 or CXCR4 receptor, then the linker is not a polymethylene group;

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(d) when the multibinding compound comprises two ligands having a hexestrol moiety capable of binding to an estrogen receptor, then the linker is not a polymethylene group;

5 (e) when the multibinding compound is capable of binding to an α -adrenergic receptor, then a ligand is not N,N'-(bis-(5-aminopentyl)cystamine (APC) or an analog thereof;

(f) when a first ligand is 1-(aryloxy)-2-hydroxypropanolamine moiety and is capable of binding to an β - adrenergic receptor, then a linker is not a polymethylene or poly(ethyleneoxide) group;

10 (g) when a first ligand is 2-allylphenyl, 4-(2-methoxyethyl)phenyl, 1-naphthyl, or 4-methoxyphenyl moiety and is capable of binding to the β 1-adrenergic receptor, then the linker is not a Jeffamine;

(h) when a first ligand is a sLeX moiety and is capable of binding to a selectin, then the linker is not a polymethylene or poly(ethyleneoxide) group;

15 (i) when a first ligand is a mannose moiety and is capable of binding to a selectin, then the linker is not a poly(arylene) group;

(j) when a first ligand is a 2-(3, 4-dihydroxybenzyl pyrrolidine) moiety and is capable of binding to a dopamine receptor and a linker is an alkylene group, then the second ligand is not a 2-(3, 4-dihydroxybenzyl pyrrolidine) or an N-ethyl (3, 4-dihydroxyphenethyl amine) moiety; and

20 (k) when a first ligand is a 2-phenylbenzimidazole moiety and is capable of binding a dopamine receptor and a linker is an alkylene, alkenylene or arylalkylene group then a second ligand is not a 2-phenylbenzimidazole or a benzimidazole moiety.